Idiopathic Pulmonary Hemosiderosis

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• **Idiopathic pulmonary hemosiderosis is a rare condition manifested by recurrent pulmonary hemorrhage of unknown cause, diffuse radiologic abnormalities, cough, hemoptysis and moderate to severe hypochromic anemia. Diagnosis can be confirmed by iron stains of the sputum or lung aspiration or by biopsy. Prolonged spontaneous remission may occur without the use of corticosteroid therapy. Studies here reported indicated that the anemia is hypochromic and microcytic anemia of blood loss and iron deficiency, in spite of the presence of large amounts of iron in the pulmonary tissue. Correction of the anemia by intensive iron therapy and transfusion is considered an important part of therapy.**

IDIOPATHIC PULMONARY HEMOSIDEROSIS is a rare condition affecting both children and adults. The authors have had opportunity to observe two patients with this condition. One patient had onset of symptoms in his teens and the other in early infancy. A brief review of the literature concerning this interesting condition is presented, together with a description of the cases observed by the authors and some comments concerning the hematological aspects of the disease.

History

In 1850, Virchow[24] first described, in autopsy specimens, a condition of brown induration of the lungs. Ceelen,[7] in 1931, was the first to describe the clinical course of the disease, in two cases, and the observations at autopsy. In 1948, Wylie[27] collected reports of 17 cases from the literature and reported an additional seven. With the exception of one 38-year-old man, the patients in all the 24 cases were children. In 1956, Wynn-Williams and Young[28] collected reports of 50 cases from the literature. Fifteen of the patients were adults, and they added a report of a case in an adult. Since that time, 19 more cases have been reported in the English language literature,[13,17] 11 in adults and eight in children.

Symptoms

Cough and hemoptysis are the predominant pulmonary symptoms. In infants and young children, the blood is swallowed and the manifestation may be in the form of vomited blood or melena. In acute episodes, cyanosis, tachycardia, fever, dyspnea and occasionally jaundice are evident. Clubbing of the fingers is sometimes present, and sometimes pallor consistent with a degree of anemia. The lungs may seem quite normal upon physical examination even in the presence of decided radiologic abnormality.

Roentgenographic Observations

Schaar and Rigler[19] said that hemosiderin can be detected in the lungs by x-ray examination in only two conditions, mitral stenosis and idiopathic pulmonary hemosiderosis. The x-ray findings have been described by Elgenmark and Kjellberg[9] as follows: "Diffuse shadows of increased density scattered more or less all over both lung fields and absolutely independent of the borders of the lobes. In some cases, there is a tendency to become denser at the bases; this cloudiness, however, often alternates with mottling of a mossy appearance in the early stages of the disease, as well as in the remissions. The mottling is the dominating feature."

Fleischner and Berenberg,[10] in 1954, gave the following x-ray description: "Diffuse opacities with reticular design rather than mottled, with emphasis on the flecklike consolidations such as are seen in miliary tuberculosis." It is evident, however, from a perusal of the descriptions given in the published reports that there is no pathognomonic or uniform roentgenographic manifestation. Diffuse or patchy densities, massive consolidations, miliary infiltrations and fine diffuse reticulonodular infiltration have all been described.

Hematology

Anemia is present at some time in all cases although spontaneous remissions may occur (Gluck).[12] The anemia is hypochromic, microcytic, and characteristic of iron deficiency due to chronic loss of blood. Reticulocytosis, hyperbilirubinemia, hyperurobilinogenuria, presence of nucleated erythrocytes in the peripheral blood, occasional positive reaction to a Coombs test and the presence of cold agglutinins have suggested the presence of hemolysis.

Clinical Course of the Disease

The clinical course is characterized by remissions and exacerbations. Anemia may improve spontaneously but the roentgenographic manifestations, once

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abnormal, never return to normal although acute massive infiltrations partially resolve. The prognosis is serious. Soergel,[22] in 1957 in a review of reports of 32 cases collected from the literature which were diagnosed during life, reported that nine of the patients died, ten had active disease, five had residual symptoms and eight were symptom-free at the time of his report. The mean duration in the reported fatal cases was 2.9 years with a range of from five weeks to ten years. Patients who were less than three years of age at the time of onset had a somewhat better prognosis.

Diagnosis

Diagnosis is made by the presence of roentgenographic abnormalities, anemia and evidence of bleeding into the lungs. A number of investigators, however, (Waldenstrom, 1944[25]; Walton and Williams, 1951[26]; Steiner, 1954,[23] and Kushner, 1958[15]) have emphasized that there may be no abnormalities observed on roentgen studies even in the presence of severe anemia. The differential interpretations of the x-ray features should consider miliary tuberculosis, pneumoconiosis, heart failure, periarteritis, sarcoidosis and mitral stenosis. In the earliest reported cases the diagnosis usually was made at autopsy. Nowadays the diagnosis is considered made if typical x-ray features and anemia are present and confirmatory evidence can be obtained by means of the demonstration of hemosiderin-filled macrophages in sputum or in material washed from the stomach, or of hemosiderin-filled macrophages obtained by lung puncture.[11] It is, of course, important to consider other possible causes for the presence of these heart failure cells.

Pathogenesis

The pathogenesis of the disease is, at present, still unknown. Several theories have been advanced: Wylie[27] originally considered this to be an elastic fiber disease. In histologic studies of autopsy specimens he noted capillary stasis and heart failure cells; there were abnormalities in the elastic cells—a decrease in the elastic fibers and thickening of the fibromuscular elements in the intra-alveolar septum. Fibrous tissue was increased and elastic tissue decreased. Wylie believed that this led to a lack of distensibility, with consequent peripheral stasis in the capillary bed, leading to hemorrhage and diapedesis and the presence of hemosiderin. However, he held that since cases have been described in which there were no elastic fiber changes, it is most likely that the elastic fiber changes are not primary but are secondary to the hemorrhagic phenomena.

The second theory, advanced by Steiner,[23] is that the antigen antibody autoimmune mechanism is involved. Offered as supporting evidence is the presence of eosinophilia in the cases reported by Steiner and by Gluck.[12] In Steiner's case, some improvement followed splenectomy. The attacks became less severe and there was less anemia. However, clubbing of the fingers, roentgenographic abnormalities and cyanosis remained.

Bruwer, Kennedy and Edwards,[5] in 1956, also reported an exceptional case in which there was extensive necrotizing arteritis in the small arteries of the lungs, necrotizing arteritis in systemic arteries and active glomerulonephritis.

A third theory of pathogenesis, advanced by Soergel[22] in 1957, is as follows: It has been shown that there are periodic increases of pressure in the lesser circulation. It is possible, therefore, that this increase in pressure may affect the fine anastomotic exchange vessels between the bronchial and the pulmonary circulatory systems which, in pulmonary hypertension, are in a varicose state. Therefore, hemorrhage may occur at the points of arterial-venous anastomosis in the lungs. The cause of the increase in pressure is unknown; in fact, it has not been definitely established that this does occur in this disease.

A fourth possibility, advanced by Propst[16] in 1955, is as follows: Observing that there is an increase in acid mucopolysaccharides within the elastic fibers of the small blood vessels, he postulated that the elastic fibers are thereby weakened, the blood vessels dilate and bleeding by diapedesis occurs. Iron is liberated, and as mucopolysaccharides have a strong affinity for it, the iron becomes encrusted on the elastic fibers. This further weakens the blood vessels and the process extends to larger vessels. The actual cause of the increase in the mucopolysaccharides is unknown.

Treatment

Reports of treatment with splenectomy and with corticosteroids have been published.

Splenectomy: Wylie,[27] in one case, noted some slight improvement after splenectomy. Barlow[1] observed none. Cordeiro[8] reported cure in two cases. However, both patients had associated thrombocytopenia and it is probable that they did not have what is now considered idiopathic pulmonary hemosiderosis. Steiner[23] noted improvement in a case he reported. Thus, in only one of five reported cases of idiopathic pulmonary hemosiderosis in which splenectomy was done was there significant improvement.

Steroid therapy: A number of patients have been treated with corticosteroids. Some improvement was reported in three of them.[4,13,14] In at least five patients,[6,15,18,22] no improvement resulted. In view of the frequency of spontaneous remission, no definite conclusions can be drawn.

CASE 1. The patient, a Caucasian male, was observed to be anemic at the age of 17 when he was examined because of fatigue and pallor. He was given a transfusion of one pint of whole blood, then was treated with iron by mouth and injection. The hemoglobin content did not reach normal levels. A year later he was rejected by the army because of anemia. The first episode of gross hemoptysis occurred at age 20. It lasted two days. X-ray films of chest and sputum studies at that time were reported to show no abnormality. Two years later, wishing to enlist in the army, the patient took double the recommended amounts of iron tablets and "just passed the examination." During his first week of basic training, he started coughing up blood and became fatigued. He was put in Letterman General Hospital and there in a period of a year numerous investigations, including bronchography and bronchoscopy, were carried out. At the end of that time, the patient was discharged from the hospital and from the army with a diagnosis of "ill-defined condition manifested by severe hypochromic anemia; hemoptysis; foamy, greasy stools and bizarre pulmonary appearance of both lower lobes as visualized by x-ray." Thereafter he had several episodes of gross hemoptysis and again became anemic.

He was first seen by the authors in 1952, at the age of 23, because of weakness and anemia. The family history was negative for the presence of either anemia or hemoptysis. One sister had been rejected as a blood donor. For most of his life he had had varying symptoms referrable to the gastrointestinal tract, usually consisting of episodes of vomiting, cramping, abdominal pains and bouts of diarrhea characterized by liquid stools, which were frequently foamy, light in color and foul-smelling.

Upon physical examination the patient was observed to be pale, well-developed and well-nourished. Breath sounds were normal and no rales were heard. Heart sounds were normal except for a faint soft systolic murmur at the apex. Blood pressure was 125/70 mm. of mercury. A summary of the laboratory examinations is shown in Table 1. In the subsequent six months, the patient received two blood transfusions because of increasing anemia. Figure 1 shows typical x-ray films of the chest in this case. Following pronounced hemoptysis, bronchoscopic examination was carried out but no abnormalities were seen in the visible tracheobronchial tree except for fresh blood which appeared to be coming from the right lower lobe bronchus. Roentgenographic films of the entire gastrointestinal tract and an intravenous pyelogram were all within normal limits. No abnormality was seen in a sigmoidoscopic examination. Erythroid hyperplasia was noted in a specimen of bone marrow but otherwise the examination did not help in diagnosis.

TABLE 1.—*Data on Laboratory Tests in Two Cases of Idiopathic Pulmonary Hemosiderosis.*

	Case 1	Case 2
Hemoglobin	5.4 gm.	7.9 gm.
Erythrocytes	3.29 (10^6)	4.89 (10^6)
Packed cell volume	24 per cent	28 per cent
Mean corpuscular hemoglobin	17 mcmg.	16 mcmg.
Mean corpuscular volume	73 cu. microns	57 cu. microns
Mean corpuscular hemoglobin content	23 per cent	28 per cent
Reticulocytes	2.6 per cent; 4.4 per cent	2.8 per cent; 3.8 per cent
Urinalysis	Normal	Normal
Icterus index	3.2 units	.....
Serum iron	46 gamma per cent; 34 gamma	.....
Total iron binding capacity	499 mcg.	.....
Iron saturation	6.8 per cent	.....
Glucose tolerance	Normal	Normal
Stool	Occult blood	Occult blood
Sickle cell preparation	.....	Negative
Hemoglobin electrophoresis	.....	A-A
Prothrombin	100 per cent	80 per cent
Prothrombin consumption	Normal	.....

In December, 1952, a diagnosis of idiopathic pulmonary hemosiderosis was considered. In March, 1953, severe hemoptysis occurred, the patient estimating that he had lost at least a pint of bright blood. He continued to raise small amounts of rust-colored sputum which, on microscopic examination, showed large numbers of macrophages containing large amounts of hemosiderin as stained by the Prussian blue reaction (Figure 2). In the ensuing two years, the patient several times had severe hemoptysis associated with sharp decreases in hemoglobin, requiring either oral or parenteral iron therapy. After January, 1955, hemoptysis occurred much less frequently than previously and it was never of such severity as to cause a decrease in hemoglobin content of the circulating blood. The clinical course is summarized in Chart 1. The patient was free of symptoms until August, 1955, when he began complaining of mild, intermittent shortness of breath. The vital capacity was normal. The arm-tongue circulation time was slightly prolonged. An electrocardiogram was interpreted as consistent with left bundle branch block. It was our impression that the patient was not in congestive heart failure and he was treated with mild sedation, which partially ameliorated the symptoms. Nine months later a complete pulmonary

function study was carried out at the Cardio-Respiratory Laboratory of the University of Southern California School of Medicine, with the conclusion that the dyspnea could not be accounted for on the basis of the decreased pulmonary function. There was slight desaturation of the arterial oxygen, slight prolongation of circulation time and an abnormal response to the Valsalva maneuver, all suggesting that the dyspnea may have been due to mild cardiac decompensation. The patient, however, continued to do well. He had no cardiac enlargement and digitalization was not required. These factors led us to conclude that he did not have primary cardiac disease. He was last examined on July 8, 1959, following an episode of mild hemoptysis, and no significant changes from the previous conditions were

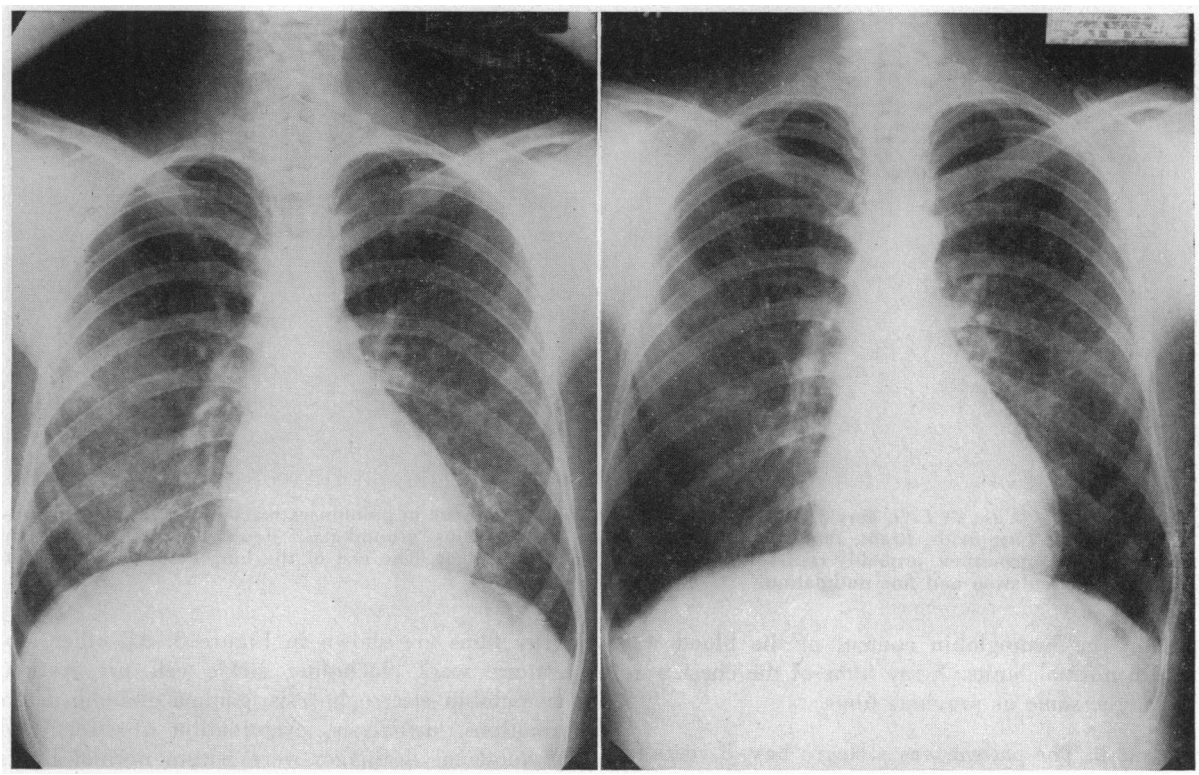

Figure 1.—(Case 1) *Left*, December 11, 1952. There is a very fine reticulated appearance of the lung parenchyma, symmetrical in distribution involving the lower two-thirds of both lung fields. *Right*, July 8, 1959, virtually no change in appearance since previous examination.

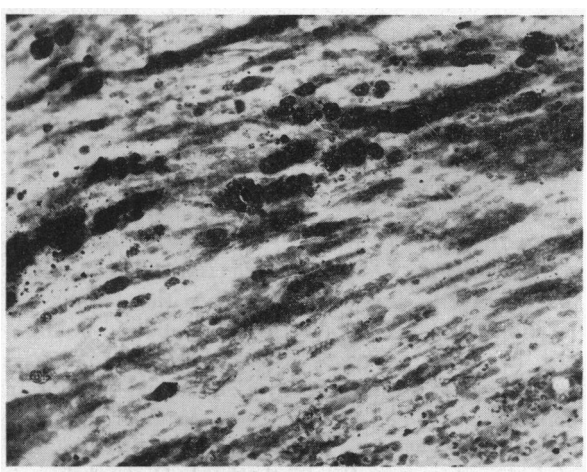

Figure 2.—(Case 1) Specimen of sputum (Prussian blue stain). Large numbers of macrophages loaded with hemosiderin granules are present. ×500.

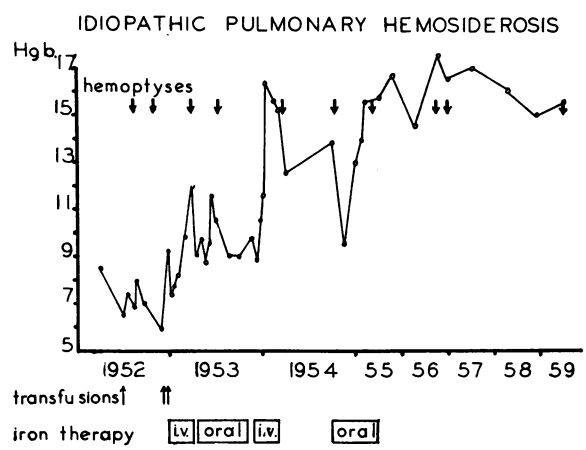

Chart 1.—Serial hemoglobin determination related to hemoptysis and therapy.

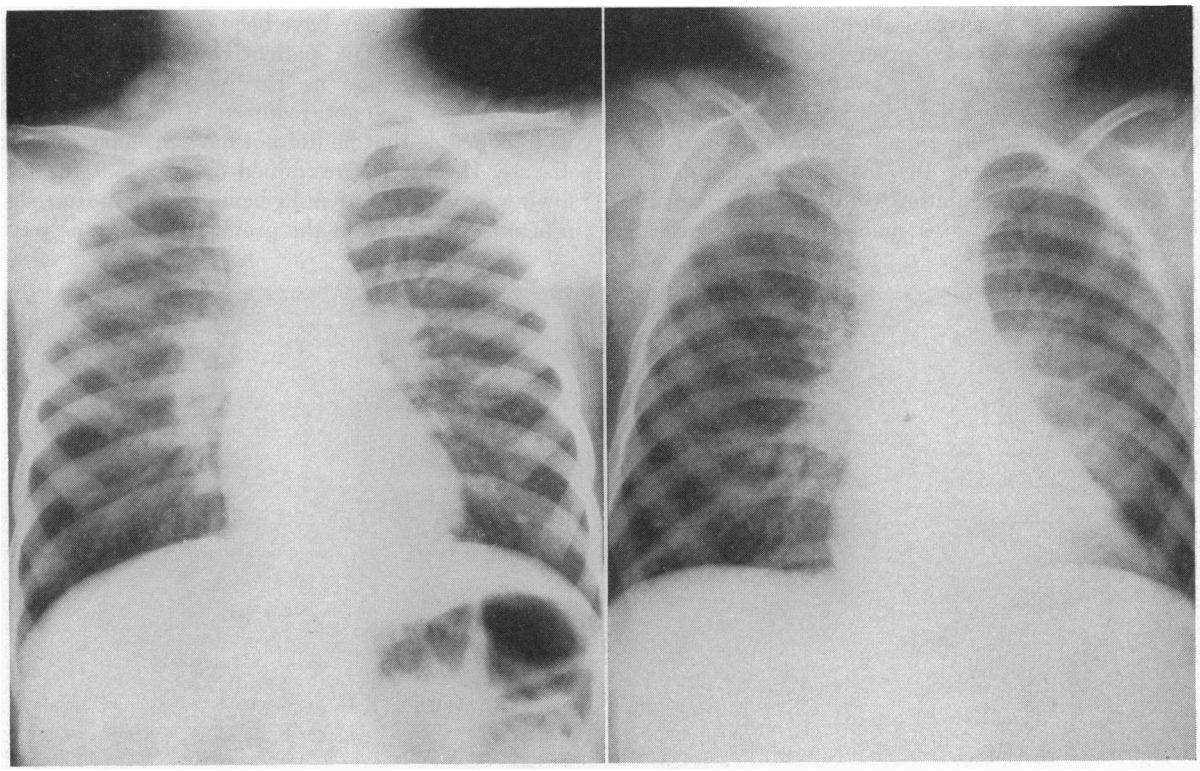

Figure 3.—(Case 2) *Left,* May 26, 1958. There is a non-specific increase in pulmonary markings in the central two-thirds of both lung fields. *Right,* January 7, 1959. There is a homogeneous "ground glass" density in the lower portion of the left hilar complex, probably representing site of rec ent hemorrhage. The rest of the lung fields show a slight degree of reticulation and fine nodulation.

noted. The hemoglobin content of the blood was within normal limits. X-ray films of the chest were about the same as previous films.

CASE 2. The patient was a Negro boy, 3 years of age when last observed, with a history of normal prenatal course and birth. He weighed 7 pounds 5 ounces at delivery. His mother died of post-partum hemorrhage. The child remained in the hospital for three weeks following birth because of excessive vomiting. He then was well until, at about the age of six months his physical development slowed, his weight increasing only 2 pounds in the next 9 months. He also had repeated respiratory infections, which were treated repeatedly with antibiotics without significant response. By one year of age, the child showed clubbing of the fingers and diminished gluteal mass and he was admitted to Kaiser Foundation Hospital, Los Angeles, for investigation. He was thin and appeared to be chronically ill. The lungs were clear to auscultation. There were no abnormal heart sounds. His physical appearance was typical of fibrocystic disease. It was learned that he had had frequent episodes of coughing and wheezing.

The hemoglobin content ranged from 7.7 to 9.2 gm. per 100 cc. (see Table 1). Examples of typical x-ray films are shown in Figure 3. All other laboratory work, including sickle cell preparation, hemoglobin electrophoresis, gamma globulin determinations, urinalysis, examination of sweat and of duodenal drainage, were within normal limits (Table 1).

The child had been admitted to hospital four more times in the first 15 months of life, at first for diagnostic study because of vomiting and chronic respiratory infection; and large, foul-smelling stools; then because of wheezing. During the stay in hospital at the age of 15 months, the patient had had "coffee ground" vomitus and tarry stools. No abnormalities were seen in x-ray studies of the upper gastrointestinal tract and the colon. Only a slight decrease in hemoglobin occurred at that time, the patient having been treated immediately with transfusions of blood and injection of iron intramuscularly. In January 1959, when the patient was 19 months old, the diagnosis of idiopathic pulmonary hemosiderosis was considered, and material washed from the stomach was observed to contain hemosiderin-filled macrophages. In March, 1959, thoracentesis was carried out and a small amount of pink-tinged material was obtained. On staining, it showed the presence of hemosiderin-filled macrophages. After the procedure a total of 10 cc. of iron

dextran* was given intramuscularly. For the next four months, the child had frequent episodes of vomiting of brownish gastric contents, and of passing black, tarry stools. The hemoglobin did not fall below 9.6 gm. per 100 cc. The patient was put in hospital four more times for vomiting, dehydration, fever and "asthma." He was not seen again for a period of six months—until January, 1960. At that time, at age 34 months, he had mumps and again had tarry stools. He was admitted to the Contagious Disease Unit of the Los Angeles County General Hospital. Blood examination there showed mild normochromic anemia (hemoglobin 10.6 gm. per 100 cc.) and a reticulocytosis of 4 per cent. X-ray films of the upper gastrointestinal tract and colon were normal. Melena ceased shortly after admission and no transfusions were necessary. In a telephonic communication with a parent in February, 1960, it was learned that the child was still not thriving and had frequent vomiting and apparent abdominal pain. Also, he had frequent respiratory tract infections.

DISCUSSION

Both cases illustrate characteristics of this syndrome in infants and adults. It is evident that prolonged spontaneous remissions may occur without the use of corticosteroid therapy. From these studies no additional information was obtained to clarify the pathogenesis of the pulmonary bleeding. It is our opinion, however, that the anemia in these cases is classical hypochromic microcytic anemia of iron deficiency due to chronic loss of blood, and that it responds to therapy with either oral or parenteral administration of iron. The paradox of a total body iron deficiency while one organ is overloaded with iron-containing pigment may be explained on the basis that the iron present in the lung is contained in hemosiderin-filled macrophages which are present predominantly in the alveoli or bound by a dense fibrous reaction in the interstitial tissues. This iron is not available for utilization by the bone marrow for hemoglobin synthesis. The laboratory findings of reticulocytosis, erythroid hyperplasia of the bone marrow, and peripheral blood normoblastosis, which suggest hemolysis, can be explained on the basis of response of the bone marrow to acute loss of blood. The increased amounts of bilirubin in the blood and urobilinogen in the urine may result from degradation of the heme pigments following the extravasation of blood into the alveoli. Similar changes, for example, are seen after massive hemorrhage into the pleural or peritoneal cavities or into large connective tissue spaces.

*Providing the equivalent of 50.0 mg. of elemental iron in each cubic centimeter.

It is our opinion that correction of the anemia by intensive iron therapy and transfusion, when indicated, is an important part of the therapy of these cases.

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REFERENCES

1. Barlow, A. D.: Pulmonary hemosiderosis, Proc. Roy. Soc. Med., 39:131-132, 1946.

2. Boyd, D. H.: Idiopathic pulmonary hemosiderosis in adults and adolescents, Brit. J. Dis. of the Chest (London), 53:41-51, January 1959.

3. Brook, N. H., and Kenealy, W. L.: Idiopathic pulmonary haemosiderosis: report of a case, New Zealand Med. J., 57:(322) 608-610, December 1958.

4. Browning, J. R., and Houghton, J. D.: Idiopathic pulmonary hemosiderosis, Am. J. Med., 20:374-382, March 1956.

5. Bruwer, A. J., Kennedy, R. L., and Edwards, J. E.: Recurrent pulmonary hemorrhage with hemosiderosis. So-called idiopathic pulmonary hemosiderosis, Am. J. Roentgenol., 76:98-107, July 1956.

6. Burckhardt, D., and Vogel, C.: Ein betrag zur idiopathischen Lungenhaemosiderose, Monatschr. Kinderh., 103:455-460, October 1955.

7. Ceelen, W.: Die Kreislaufstörungen der Lungen. In Henke-Lubarsch: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, J. Springer, Vol. III/3, pp. 1-163, 1931.

8. Cordeiro, M.: Un cas d'hemosiderose pulmonaire idiopathique queri par splenectomie, Helvet. Pediat. acta, 7:501-507, November 1952.

9. Elgenmark, O., and Kjellberg, S. R.: Hemosiderosis of the lungs—typical roentgenological findings, Acta radio, 29:32-36, 1948.

10. Fleischner, Felix G., and Berenberg, Arnold L.: Idiopathic pulmonary hemosiderosis, Radiology, 62:522-526, April 1954.

11. Gellis, S. S., Reinhold, J. L. D., and Green, S.: The use of aspiration lung puncture in the diagnosis of idiopathic pulmonary hemosiderosis, A.M.A. J. Dis. of Children, 85: 303-307, March 1953.

12. Gluck, E.: Idiopathic pulmonary haemosiderosis. Report of a case, with special regard to the pathogenesis, Acta Path. et Microbiol. Scand., 37:241-251 (Fasc. 3), 1955.

13. Gurewich, V., and Thomas, M. A.: Idiopathic pulmonary hemosiderosis in pregnancy. Report of a case suggesting early pulmonary hemosiderosis with clinical recovery after steroid therapy, N.E.J.M., 261:1154-1159, December 3, 1959.

14. Irvin, J. M., and Snowden, P. W.: Idiopathic pulmonary hemosiderosis; report of a case with apparent remission from cortisone, A.M.A. J. Dis. Child., 93:182-187, February 1957.

15. Kushner, D. S., and Szanto, P. B.: Diagnostic problems. Hemolytic and hypochromic anemia and elevated cold agglutinin titer in a seven-year-old child, J.A.M.A., 168: 1013-1018. October 1958.

16. Propst, A.: Morphologie und Pathogenese der Essentielden Lungenhaemosiderose, Virchows Archiv fur Pathologische Anatomie und Physiologie, 326:633-663, 1955.

17. Russi, S., and Wingo, C. F.: Idiopathic pulmonary hemosiderosis, Am. J. Path., 32:611, May-June 1956.

18. Sandoe, E.: Essential pulmonary haemosiderosis; account of two cases, one treated experimentally with ACTH, Danish M. Bull., 1:175-179, November 1954.

19. Schaar, F. E., and Rigler, L. G.: Idiopathic pulmonary hemosiderosis; essential brown induration of lung; report of case and review of literature, Journal-Lancet (Minn.), 76:126-134, May 1956.

20. Schoeniger, E. L., Tucker, A. S., and Bolande, R. P.: Idiopathic pulmonary hemorrhage with hemosiderosis and microcytic anemia, Radiology, 70:191-195, February 1958.

21. Smith, W. E., and Fienberg, R.: Early nonrecurrent idiopathic pulmonary hemosiderosis in an adult; report of a case, N.E.J.M., 259:808-811, October 1958.

22. Soergel, K. H.: Idiopathic pulmonary hemosiderosis; review and report of two cases, Pediatrics, 19:1101-1108, June 1957.

23. Steiner, B.: Essential pulmonary haemosiderosis as an immuno-haematological problem, Arch. Dis. Child., 29: 391-397, October 1954.

24. Virchow, R.: Die Krakhaften Geschwulste, Berlin Aug. Hirshwald, Part 2: 1864 Monograph.

25. Waldenstrom, J.: Relapsing, diffuse, pulmonary bleedings or hemosiderosis pulmonum—a new clinical diagnosis, Acta Radiol., 25:149-162, 1944.

26. Walton, M., and Williams, A. A.: Idiopathic pulmonary haemosiderosis. Report of a case in an adult, Brit. M. J., 2:390-391, Aug. 18, 1951.

27. Wylie, W. G., Sheldon, W., Bodian, M., and Barlow, A.: Idiopathic pulmonary haemosiderosis (essential brown induration of the lungs), Quart. J. Med., 17:25-48, January 1948.

28. Wynn-Williams, N., and Young, R. D.: Idiopathic pulmonary haemosiderosis in adult thorax, 11:101-104, June 1956.